Since the 1990s, scientists have had the ability to manipulate genes of interest and study the resulting effects. Genetic therapies have tremendous potential for treating genetic diseases and mutations with debilitating consequences (e.g., Huntington's disease and fatal familial insomnia), but initial attempts to treat genetic diseases like severe combined immunodeficiency resulted in leukemia in many patients who received the experimental treatments. Continued advances in the gene therapy field have resulted in the development of the newest (and potentially most influential) genomic modification technique: clustered, regularly interspaced, short palindromic repeats (CRISPR).

Other processes to perform similar genetic manipulations precede CRISPR. Meganuclease techniques like zinc finger nucleases and transcription activator-like effector nucleases use complex protein-DNA interactions to edit a gene of interest, and successfully modified cells require a tedious selection process to remove their unaltered counterparts. Therapies such as haematopoietic-stem-cell gene therapy and T-cell immunotherapy for cancer have shown great utility but are far more constrained in their application than CRISPR.

The enormous potential of CRISPR comes from its broad applicability: Using simple RNA base-pairing rules, CRISPR is capable of cleaving any target sequence and introducing random mutations (by non-homologous end joining) or specific mutations through the co-injection of engineered DNA constructs with homology that matches the cleaved ends of the original DNA. By completely avoiding the arduous transfection/selection process – since in-vivo CRISPR yields germline mutations that can be passed to future generations without repeated gene knockdown – CRISPR allows for one-time embryonic gene editing. The mechanism by which CRISPR targets certain DNA sequences (guide RNA or gRNA) also allows for multiplexed treatment, where several gRNA sequences can be included at one time to edit multiple genes simultaneously.

While these improvements may appear to some scientists as the keys to effective and sustainable gene therapy, CRISPR’s potential for non-interventional application raises serious concerns in the scientific and philosophical communities. The question of how far to take CRISPR in terms of what might be considered an acceptable desired outcome comes to the forefront; although “science-fiction scenarios of human breeding” are highly unlikely, widespread CRISPR usage is described by many experts in gene therapy as “largely inevitable.” The human genome belongs to everyone: Does that ownership constitute the right to modify the genome?

As of 2015, there are over 25,000 annotated genes, with more than 3,000 genetic mutations linked to disease phenotypes. CRISPR’s simple design, efficient gene modification, and multiplexing ability make it an incredible tool by which these diseases could be mitigated or eliminated. Although further optimization is required, any organ or cell population could eventually be targeted with CRISPR, making a number of diseases – previously difficult (or impossible) to treat – curable. CRISPR is not without technical limitations, nor is it immune to inaccuracy: Off-target effects on a genome-wide scale could produce unpredictable immediate or long-term effects, and incomplete gRNA targeting could yield mosaics (where a single zygote results in multiple genetically distinct cell types) or chimeras.
(where unmodified and modified embryos fuse to produce a single organism with both cell types), both of which can result in a worsened phenotype [1, 7].

The unknown long-term effects of off-target modification (or producing multiple alleles by mutating cells differently from the same target constructs) are of dire ethical concern [10]. Even if a patient's therapy with CRISPR is successful, some potential exists for unpredictable effects on future generations. Quick, cheap repairs for genetic mistakes are attractive but using CRISPR to inadvertently (or intentionally) destroy genetic diversity or infringe on the rights of the unconceived and unborn would be classically human tragedies [5, 8]. The alternative is tragic in itself; possessing, but not utilizing, a tool by which painful and fatal diseases could be treated might also be considered unethical [5].

Another side to the ethical debate surrounding CRISPR exists: Modifying our own genome presents a profound transformation in humanity's relationship with nature [8]. Like H.G. Wells' classic *The Island of Doctor Moreau*, strange modifications (sans vivisection) to humanity could be made without medical intent. While regulatory agencies monitor research in the Western world closely, Chinese scientists have already begun modification of human embryos and there are reports of more human experimentation with CRISPR throughout Asia [4]. The fear of "designer baby" production leading to unanticipated genetic anomalies in future generations is a real one; some cynical scientists believe broad CRISPR application to be a matter of "when, not if" [1], but the debate on gene modification regulation rages on.

CRISPR falls into the category of biomedical engineering, so the Biomedical Engineering Society Code of Ethics (BMECoE, underlined text is hyperlinked) is a sensible choice when analyzing CRISPR's ethical considerations. The BMECoE is separated into four categories: professional obligations, healthcare obligations, research obligations, and training obligations. Most applicable to CRISPR are the healthcare obligations: (1) regard responsibility toward and rights of patients, including those of confidentiality and privacy, as their primary concern and (2) consider the larger consequences of their work in regard to cost, availability, and delivery of healthcare – and the first research obligation: (3) comply fully with legal, ethical, institutional, governmental, and other applicable research guidelines, respecting the rights of and exercising the responsibilities to colleagues, human and animal subjects, and the scientific and general public.

BMECoE item (1) regarding the rights of the patient as a primary concern pertains to the "immediate" effect of CRISPR therapy – *i.e.* does the CRISPR treatment resolve the undesirable genetic anomaly without creating a new problem? – is relatively satisfied with current mouse models [7] although further technical challenges requiring circumvention still exist. This ethical code protects patients and, while inarguably important, is not as applicable at the current level of CRISPR use as the other highlighted items from BMECoE.

Item (2), considering the larger implications of CRISPR usage in terms of the cost, availability, and delivery of healthcare, is more relevant to the "future generation" ethical dilemma CRISPR presents. If undesirable long-term or multi-generation CRISPR effects exist, any cost benefit of CRISPR might be negated by the eventual (potentially generational) treatment expenses. Alternatively, in terms of the availability and delivery of healthcare, CRISPR could be used to mitigate cultural misuses of medicine like the abortion of female fetuses in communities where male babies are more desirable [6].
The third highlighted item from BMECoE is perhaps the most interesting: Complying with the applicable legal, ethical, institutional, and governmental guidelines for CRISPR use (on humans) is essentially the heart of the modern CRISPR dilemma, as no such guidelines currently exist. Regulatory agencies like the FDA, in combination with the grant application process, exist to moderate research projects. Whether CRISPR projects relating to human embryo modification will continue is unknown, but continued discourse has revealed a few possible approaches through minimalist, due-care, and good-works perspectives.

A minimalist approach is bare-bones: For CRISPR use on human embryos, a simple regulation like "CRISPR has to be safe for the patient whose genotype it immediately alters" is the broadest, least specific possible option. Due-care perspectives, which incorporate a preventative aspect, would include regulations such as "CRISPR can only be used to restore a common wild-type allele" (e.g. restoring functional fertility genes to an embryo, but not deactivating these genes), protecting patients from the types of genetic manipulation that are reminiscent of eugenics. The good-works model, which goes "above and beyond" simple due-care protections, might reach beyond the immediate patient: "CRISPR can only be used if it has no ill multi-generational effects". Because of the CRISPR technology's youth, little long-term data is available, and no multi-generational human studies are currently possible.

Whether humanity (with regard to CRISPR) should "surrender to the rule of technology or commit to a more responsible steering of the course of progress" seems obvious – some regulations will ultimately be necessary. In 2015, Nobel laureates and other scientists from Stanford and Caltech proposed a moratorium on germline gene (progeny-affecting) editing, with the concern that multi-generational effects would prove detrimental to healthcare. The group cited the 1975 Asilomer conference (which was attended by many of the scientists now proposing the moratorium), which promotes "responsible self-regulation" and effectively demands that the public defer to scientists in their understanding of emerging technologies. Jasanoff argues that Asilomer is inappropriate for CRISPR decision-making, instead suggesting that the public "help steer study and deliberation in more democratic directions: envisioning futures, distribution, trust, and provisionality".

While the public offers multidisciplinary expertise, the Greek aphorism "know thyself" reminds those who might provide CRISPR therapies of their primary directives. Since it is the duty of healthcare professionals to mitigate suffering and mediate disease, some CRISPR supporters advocate for the development of a "translational framework," whereby the therapy can be justified ethically through the alleviating results it provides. Such a framework may allow for multigenerational suffering, but the immediate effects of CRISPR treatments would be well-understood and potential for study would not necessarily be restricted.

Where the Asilomer perspective suggests that the CRISPR regulation dilemma be resolved entirely by scientists and the "translational framework" approach allowing for a collaboration between medical professionals and the public, some lobbyists demand a regulatory system removed from scientists. Sarewitz mentions that "the sciences of the existential should be made collectively" and that "scientists are not elected, and cannot represent cultural values," going as far as to compare the potential danger of AI to the implications of human CRISPR modification. Politicians, he argues, are free from conflicting data (e.g. an agricultural biologist and an ecologist will bring opposing perspectives to a GMO-farming case) and are better suited to make ethical decisions. Some scientists agree, and take an ambivalent approach: "we are scientists, not philosophers". Regardless, the same regul-
lations do not apply everywhere and, as evidenced by the ongoing human embryo CRISPR research in China, it is likely too late to fully restrict germline gene modification.

The "other-shoe" test allows for a personal ethical analysis: In imagining that you are affected by a disease that CRISPR could treat, the three perspectives can be explored. Asilomer, in prohibiting broad CRISPR application, would be the most frustrating of the approaches; as Sheridan discusses, not resolving an issue when the technology is available could be considered unethical [8]. Depending solely on politicians to make decisions concerning the ethics of gene manipulation is equally concerning [8] – suffering from horrific genetic anomalies as a consequence of political meddling would be highly undesirable.

By process of elimination and an empathetic perspective, the "translational framework" model appears to be the best solution. Collaboration between medical professionals, legislators, and the public would likely promote the interests of those most affected by CRISPR therapies while maintaining an emphasis on ethical behavior. Fortunately, this outcome is by far the most likely: With such tremendous potential for to advance genetic science and healthcare, CRISPR proves to be an exciting new technology that will face great scrutiny from a multitude of agencies in the regulatory process.

References


